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Recombinant Human Monoclonal Antibodies Casirivimab/Imdevimab use in Inhibition of the Sars-Cov-2 Virus Infection

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ABSTRACT

Introduction: The spread of the SARS-CoV-2 virus has caused severe problems for healthcare facilities and infrastructure worldwide. The development of rapid diagnostic tools, effective treatment protocols, and vaccines against the pathogen has accelerated. This work aims to elucidate the benefits of recombinant human monoclonal antibodies to slow the progression of SARS-CoV-2 variant B.1.617.2 infection (delta variant).

Material and methods: This is a retrospective analysis with a 6-month follow-up involving all patients who received recombinant human monoclonal antibodies (MABs) Casirivimab/Imdevimab at University Hospital Martin in November and December of 2021.

Results: A total of 180 patients were enrolled in the cohort with a mean time to administration of symptoms were 6.01 ± 0.3 days in the group of vaccinated patients and 5.52 ± 0.28 days in the group of non-vaccinated patients and a mean time to the resolution of symptoms were 4.37 ± 0.62 days in the group of vaccinated patients and 3.83 ± 0.3 days in the group with non-vaccinated patients. Of these patients, 13 developed bronchopneumonia (7.2%)-serious side effects after MAB administration were observed in 1 patient.

Conclusion: Using recombinant human monoclonal antibodies Casirivimab/Imdevimab to slow or to stop SARS-CoV-2 variant infection B.1.617.2 significantly affected the course of the disease. Quick diagnostics, identification of at-risk patients, and multidisciplinary collaboration are essential in COVID-19 management.

Keywords: SARS-CoV-2; Monoclonal antibodies; Casirivimab/Imdevimab

INTRODUCTION

In 2019, the SARS-CoV-2 virus, the causative agent of COVID-19, was identified for the first time. The SARS-CoV-2 virus enters host cells, such as nasal/bronchial epithelial cells or pneumocytes, by binding through its spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface. After the penetration of the virus into the host's organism, the disease develops in various forms, from an asymptomatic course to the development of a severe course of the disease with multi-organ involvement and respiratory insufficiency, often with the need to use pulmonary ventilation or use of the

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extracorporeal circulation (ECMO). Recent data show that a more severe course of COVID-19 is associated with a high viral load in the host [1-3].

Thanks to vaccination, we can observe a decline in cases with a moderate to severe course that requires hospitalization. In addition, the administration of the monoclonal antibodies Casirivimab/Imdevimab, the use of which was first approved by the Food and Drug Administration (FDA) in November 2020 in the United States of America (USA) and later in other countries, was a significant help in preventing the development of a severe course of COVID-19. MABs were approved by FDA for emergency use to treat mild to moderate cases of COVID-19. Recombinant human monoclonal antibodies Casirivimab and Imdevimab combine two gamma one immunoglobulins that act against the spike protein of the SARS-CoV-2 virus, the causative agent of the disease COVID-19.

They show a high affinity for binding to different non-overlapping epitopes of the binding domain of the receptor (VDR) for the spike protein of the SARS-CoV-2 virus [4,5]. Each antibody almost entirely (≥ 95%) blocks *in vitro* binding of the VDR spike protein of SARS-CoV-2 to the human angiotensin-converting enzyme 2 (ACE2) receptor [5]. Casirivimab and Imdevimab block the binding of the spike protein of the virus to ACE2 already with a half maximum inhibitory concentration of 56.4 pmol/l and 165 pmol/l individually and 81.8 pmol/l in combination [6]. In animal model studies, MABs have shown therapeutic potential when used prophylactically or as a treatment for ongoing COVID-19 infection, limiting airway viral load and virus-induced lung injury in monkeys and body weight loss in hamsters. To date, we know several variants of the SARS-CoV-2 virus, for example, B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), B.1.617.2 (delta), and others (**Table 1**).

Table 1: WHO nomenclature of the SARS-CoV-2 subtypes (6).

World Health Organization Nomenclature	
Alpha	B.1.1.7
Beta	B.1.351
Gamma	P.1
Delta	B.1.617.2
Omicron	B.1.1.529, BA.2
Epsilon	B.1.427, B.1.429
Zeta	P.2
Eta	B.1.525
Theta	P.3
Iota	B.1.526
Kappa	B.1.617.1
Lambda	C.37
Mu	B.1.621

AIMS

This work aims to elucidate the benefits of recombinant human monoclonal antibodies to slow the progression of SARS-CoV-2 variant B.1.617.2 infection (delta variant) and to determine the benefit of the MABs in the strategy of treating the COVID-19 disease. We determined the average number of days until the disappearance of the symptoms from the administration of MAB, the occurrence of adverse effects including CRS, and the frequency of the consequences of the disease COVID-19 in patients who were submitted to the MAB. Furthermore, the work aimed to determine the proportion of patients vaccinated and required hospitalization for the development of bronchopneumonia associated with COVID-19 compared to patients who were not vaccinated as other comorbidities that increased the rate of hospitalization in patients.

MATERIALS AND METHODS

MABs Casirivimab/Imdevimab were indicated for slowing or stopping RT-PCR-confirmed COVID-19 in patients aged 12 years and older who are not oxygen dependent (peripheral blood oxygen saturation >90%) and are at high-risk diseases with a severe or very severe course up to death. The infusion time with added MABs was 20 minutes-45 minutes, and the patients were monitored for at least one hour after drug administration. The administration of MAB is associated with the occurrence of adverse reactions, including the occurrence of Cytokine Release Syndrome (CRS).

Therefore, the treatment was given in an outpatient form at the University Hospital in Martin, where it was possible to manage the allergic reaction to the infusion. The infusion was given once and contained 600 mg of Casirivimab and 600 mg of Imdevimab diluted in 250 ml or 500 ml of normal saline solution. Among the risk factors of patients who were indicated for MAB administration were age over 65 years, obesity with BMI over 35 kg/m^2, existing cardiovascular disease including arterial hypertension with organ complications, chronic lung disease including asthma and Chronic Obstructive Pulmonary Disease (COPD), diabetes type 1 or 2. Other risk factors include chronic kidney disease, including the need for dialysis, kidney or other solid organ transplant status, hepatic insufficiency, use of immunosuppressive therapy, oncological diseases or chronic infections, and immunodeficiency conditions such as hepatitis or viral infection-Human Immunodeficiency Virus (HIV).

Inclusion criteria for MAB administration and HIV-Human Immunodeficiency Virus are:

- Patients older than 65 years
- Patients with BMI ≥ 35kg/m^3
- Patients chronic kidney disease (CKD G3-G5) including hemodialysis patients and patients with nephrotic syndrome
- Patients with chronic hepatic disease in the stage of fibrosis or cirrhosis with hepatic insufficiency signs
- Patients with cardiovascular disease with heart failure or cardiac decompensation in the past

- Patients with arterial hypertension with organ complications
- Patients with chronic pulmonary diseases and chronic respiratory insufficiency or with exacerbations requiring hospitalization in the past
- Patients with diabetes mellitus type 1 or 2 with complications
- Patients with the severe form of Parkinson's disease or with other neurological diseases with the risk of respiratory failure during COVID-19. Patients with severe cases of immunodeficiency or Down syndrome with obesity or other severe complication associated with Down syndrome
- Patients with immunodeficiency
- Patients with hemato-oncological therapy after organ transplantation, or after transplantation of the hematopoietic cells
- Patients with badly controlled HIV infection or on immunosuppressant's

Statistical Analysis of Data

We evaluated all data using descriptive statistics, with data normality (normality of data distribution) assessed using the Shapiro-Wilk test. In addition, we evaluated differences between groups using the Student's T-test for parametric testing and the Mann-Whitney U-test for non-parametric group testing. To assess the correlation between groups, we chose the Pearson correlation coefficient. A value of $p<0.05$ and 0.001 in the analysis was considered statistically significant. For statistical data processing, we used commonly available statistical tools on the Internet and the MDCALC program, version 20.2.15.

RESULTS

A total of 180 patients were enrolled in the cohort, of which 82 were vaccinated, and 98 patients did not receive any of the SARS-CoV-2 vaccines before MAB administration. The groups were made up of 61.76% women and 38.24% men. A total of 60 patients (33.3%) used antibiotics along with supportive therapy, of which eight patients using ATB developed bronchopneumonia (BRPN), and three were hospitalized (p=0.32). In 5 patients with BRPN, treatment did not include added ATB. Bronchopneumonia occurred in a total of 13 patients (7.2%), of which four patients were vaccinated, nine patients were not vaccinated with any vaccine against SARS-CoV-2 (p=0.13), of which three were vaccinated (3.7%). 6 unvaccinated (6.1%) patients required hospitalization for the progression of respiratory insufficiency (p=0.23). A total of 4 vaccinated (4.9%) and 8 unvaccinated (8.2%) patients were hospitalized for the advancement of chronic diseases during SARS-CoV-2 infection (p=0.07). The mean time to administration of symptoms were 6.01 ± 0.3 days in the group of vaccinated patients and 5.52 ± 0.28 days in the group of non-vaccinated The mean time to the resolution of symptoms were 4.37 ± 0.62 days in the group of vaccinated patients and 3.83 ± 0.3 days in the group with non-vaccinated patients (**Table 2**).

Table 2: Vaccinated and unvaccinated patients after MAB administration.

	Vaccinated patients after MAB administration n=82	Non-vaccinated patients after MAB administration n=98	P values (without deviation)
Age (mean ± /- SEM)	71.42 ± 1.33	70.23 ± 1.14	0.56
Sex (males)	31 (37.8%)	34 (34.7%)	0.25
Day of the onset of the symptoms	6.01 ± 0.3	5.52 ± 0.28	0.5
Day of the positive antigen test	4.63 ± 0.27	4.16 ± 0.21	0.61
Day of the symptoms relieve after MAB	4.38 ± 0.62	3.84 ± 0.3	0.33
COVID-19 associated BRPN	4 (4.9%)	9 (9.2%)	0.13
Hospital admission due to BRPN	3 (3.7%)	6 (6.1%)	0.23
Hospital admission due to other causes	4 (4.9%)	8 (8.2%)	0.07
Long COVID	12 (14.6%)	29 (29.6%)	0.02

Although there were numerically exciting findings in comparison between groups of vaccinated and unvaccinated patients in developing bronchopneumonia and need for admission to hospital due to other causes such as destabilization of diabetes mellitus or arterial hypertension, we proved the level of significance in administering long-COVID syndrome (p=0.02). One patient had a cytokine release syndrome-grade 3 requiring hospitalization. We noted the presence of various comorbidities in the patients; for example, the most common were cardiovascular diseases such as a previous myocardial infarction or arterial hypertension. Furthermore, there were type 1 or 2 diabetes mellitus, oncological diseases, most often hemato-oncological and uro-oncological diseases, chronic kidney disease in several patients with the need, and conditions associated with immunodeficiency, including induced immunodeficiency after solid organ transplantation. In the group of vaccinated and unvaccinated patients, the presence of obesity and cardiovascular diseases (overcame myocardial infarction, arterial hypertension with organ complications) showed the highest coincidence with a longer recovery time, which can be considered as inde-

pendent risk factors (Pearson coefficient 0.611) [7] (**Figure 1**).

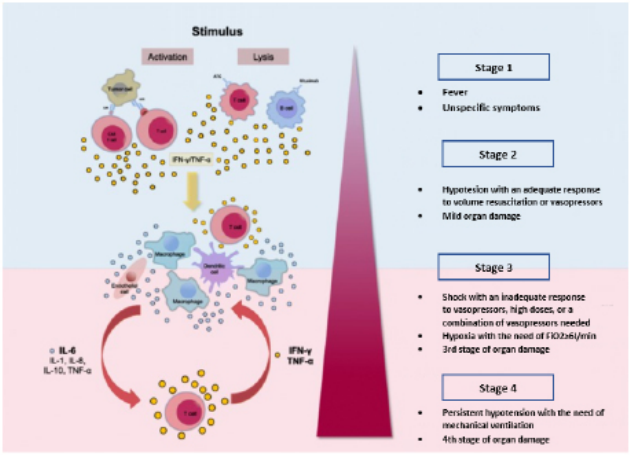

Figure 1: Activation and stages of the cytokine release syndrome. Reprinted from: Shimabukuro-Vornhagen et al. (2018). IL-6-Interleukin 6, IL-8-Interleukin 8, IL-10-Interleukin 10, TNFα-Tumor necrosis factor α, IFN-γ-Interferone γ.

DISCUSSION

In this retrospective study, we found that compared to vaccinated patients, a significant proportion of unvaccinated patients developed long-COVID syndrome or persistent post-COVID syndrome after receiving MAB (p=0.02). In the case of long-COVID, these syndromes are manifested by the persistence of typical symptomatology (dry cough, sub febrile, loss of smell or taste, weakness, brain fog, and many others) from the acute illness for four weeks and in the case of persistent post-COVID syndrome for up to several months. Most often, we noticed the loss of smell and taste or their change, as well as eating disorders, persistent cough, and weakness or so-called brain fog, which prevented the performance of everyday activities.

Several studies mention that post-COVID or long-COVID syndrome symptoms seem pretty consistent, with a higher incidence in women (14.9% compared to men 9.5%), increasing with age (age over 70 years, p=0.0005). Other factors include obesity, asthma, poor general health, poor pre-pandemic mental health, and poor socio-demographic characteristics. The impact of nationwide lockdowns, work-from-home, and restrictions on physical activity on the rising proportion of the already obese population with incorrect diet and physical activity patterns is particularly noteworthy [8-15]. A prospective study from Wuhan, including 1733 patients after overcoming COVID-19 with a 6-month follow-up, showed up to 26% incidence of sleep difficulties and 23% incidence of anxiety and depression episodes. Even though the cause of long-COVID is still not fully understood, it still affects infrastructure worldwide.

Furthermore, we found that patients with COVID-19 were more often hospitalized for exacerbation of chronic diseases (4 vaccinated and 8 unvaccinated patients) than for progression of COVID-19-associated BRPN (3 vaccinated and 6 unvaccinated patients). The difference in the number of hospitalizations in patients after and without vaccination could be caused by a higher number of comorbidities and often a combination of more comorbidities in the group of patients after vaccination than in non-vaccinated patients (p=0.07).

Cytokine release syndrome as an adverse effect of Casirivimab/Imdevimab recombinant monoclonal antibodies is a product of immune hyper activation and loss of regulation of the balance between pro-inflammatory cytokines. A study by Leisman et al. reported that elevation of inflammatory cytokines in patients with severe to critical course of COVID-19 disease (including height of IL-6) showed lower values than in patients with Acute Respiratory Distress Syndrome (ARDS) in patients without SARS-CoV-2 and in sepsis. In contrast, patients with COVID-19 have higher levels of D-dimers and C-reactive protein than other critically ill patients. The authors conclude that the overall critical course in patients with COVID-19 and elevated cytokine levels have an unclear cause. Therefore, it is necessary to consider alternative mechanisms of organ dysfunction [9].

The authors of the study Eskazan et al., present the results of administering tocilizumab (a human chimeric monoclonal antibody against IL-6) in patients with a severe course of COVID-19 accompanied by CRS, which is considered the leading cause of mortality. The monitored patients observed an increase in the levels of various indicators in a pro-inflammatory state (increase in C-reactive protein, procalcitonin, D-dimer, and others). Furthermore, early administration of tocilizumab, even before placing the patient in an Intensive Care Unit, showed success. Still, in patients with a severe course of COVID-19 and with COVID-19-associated BRPN, the administration of tocilizumab showed no benefit [10]. However, in the extensive randomized controlled trial RECOVERY (Randomized evaluation of COVID-19 therapy), tocilizumab demonstrated an improvement in survival and clinical status in patients with a severe course of COVID-19 with hypoxia and CRS, including a lower rate of use of invasive mechanical ventilation (p=0.0001) [11].

Although very rarely, allergic reactions have been observed with MAB Casirivimab/Imdevimab. These events occurred within one hour after the end of the infusion. They resolved after the administration of supportive treatment (e.g., volume

therapy in combination with oxygen therapy and the use of antihistamines without the need for subsequent hospitalization, CRS 1-2). In addition, infusion-related reactions have occurred with administering various infusion preparations containing the combination of Casirivimab and Imdevimab. The manifestations and symptoms of these reactions often included tremors, dizziness/syncope, hot flashes, nausea, and urticaria. In general, reactions occurred during or within 24 hours of infusion, were mild to moderate in severity, and resolved with over-the-counter medications (e.g., antihistamines, nonsteroidal anti-inflammatory drugs) or without intervention [4].

Collective Ganesh et al. participated in a study with the administration of MAB Casirivimab/Imdevimab in a total of 3596 patients. Patients had atleast one comorbidity that classified them in the group with an increased risk of a severe course of COVID-19. The collective identified groups of patients at higher risk of needs to visit the emergency room or hospitalization (chronic kidney disease, exacerbation of chronic lung disease) or hospitalization in the intensive care unit (cardiovascular complications). A lower risk of hospitalization has been reported in patients with a higher body mass index (BMI) [12].

A study by Abani et al. reports the average onset time of symptoms in patients with COVID-19 to be nine days on average. The p-value for the difference in patient mortality between those who received MAB and those who did not receive MAB was p=0.14; in percentage terms, the mortality of patients after MAB was 19%, and for patients without MAB, 21%. Despite the administration of MAB, 31% of patients required intensive care unit stay, and 12% of patients needed mechanical ventilation support vs. 37% of patients without MAB in ICU and 14% with mechanical ventilation support [13].

CONCLUSION

This retrospective study confirms a reduced incidence of bronchopneumonia associated with SARS-CoV-2 in patients belonging to risk groups of the population who were administered MAB, especially in patients who previously received any of the preparations of the vaccine regimens against COVID-19. We also found a lower rate of hospitalization for bronchopneumonia associated with COVID-9 in the vaccinated group. In addition, we observed a statistically significant difference between the groups of vaccinated and unvaccinated patients describing the long-covid syndrome in favor of the group after vaccination against COVID-19. Overall, casirivimab/imdevimab is a promising treatment option for high-risk patients with mild to moderate COVID-19, and its use should be encouraged in appropriate patient populations.

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None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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